Clinical Observations

A Systematic Review of RCTs and quasi-RCTs on Traditional Chinese Patent Medicines for Treatment of Chronic Hepatitis B

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Abstracts: Traditional Chinese patent medicines (TCPMs) are widely used for treatment of chronic hepatitis B (CHB) in China. To estimate the overall effectiveness of TCPMs for CHB, we performed a systematic review of clinical reports designed as randomized controlled trials (RCTs). One hundred and thirty-eight available RCTs and quasi-RCTs on 62 TCPMs, involving 16,393 patients, were included. The methodological quality of these trials was generally "poor". Few trials (6.52%) reported the methods of randomization correctly. Another common problem was the lack of allocation concealment, proper blinding, and the reporting of lost cases and dropouts. Forty-two trials (30.43%) on 27 TCPMs reported some anti-viral effect of TCPMs. Others reported beneficial aspects, including improvements of liver function (79.71% of the studies), liver fibrosis (29.99%), and CHB symptoms (92.75%). Forty-one articles (29.71%) reported mild adverse events with TCPMs but these occurred infrequently. In summary, the outcome of the report on currently registered TCPMs may be biased due to poor methodology. The data from these trials, therefore, is too weak to use in forming a recommendation for treatment of CHB. Nevertheless, five drugs (Dan Shen agents, Da Huang Zhe Chong pill/capsule, Shuang Hu Qing Gan granule, Fu Zheng Hua Yu granule and Cao Xian Yi Gan capsule) appear to be more effective than the other TCPMs.

Keywords: *chronic hepatitis B; traditional Chinese patent medicines; systematic review; quality of clinical trials*

The hepatitis B virus (HBV) causes chronic infection in approximately 400 million people worldwide. It is estimated that 50% of male carriers and 14% of female carriers will eventually die of complications from cirrhosis and hepatocellular carcinoma.[1] Interferon alpha agents, and nucleoside and nucleotide analogues are widely used for treatment of chronic hepatitis B (CHB). Nevertheless, the incomplete anti-viral efficacy and the drug-resistant phenomena of these agents are still a challenge in clinical practice and are an active area of research. HBV infection has become one of the most serious public health problems in China. The use of traditional Chinese medicine (TCM) is an appreciable distinction in the treatment of CHB between China and the western world. Traditional Chinese patent medicines (TCPMs) are developed by combining modernized pharmaceutical technologies with ancient TCM theories. Refined dosage forms and relative standardization in composing the main effective substances are considered real advantages of TCPMs compared with the traditional Chinese decoction. This combination provides the convenience of administration and allows for efficacy evaluation in clinical trials.

TCM has a long history in treating many diseases, including CHB. Although this ancient medicine is commonly thought of as complementary or alternative in the western world, it is still widely accepted in China by patients and practitioners, and used in both TCM and western medicine hospitals. Several systematic reviews have been published in English to evaluate TCM or Chinese herbs for CHB.[2-4] However, few systematic reviews of TCPMs for CHB have been made, although they already make up a considerable proportion of the medical cost for Chinese CHB patients. Moreover, the use of TCPMs is vaguely recommended in the guidelines for treatment of CHB issued by the Chinese Medical Association.[5] There is still uncertainty regarding the clinical efficacy of TCPMs for the treatment of CHB. In addition, there is confusion regarding the selection of TCPMs for patients with CHB since there is no reliable way to select the best medicine from the large pool available from so many available. Based on the challenges that exist in clinical practice, we sought to quantitatively assess the quality, and overall efficacy of TCPMs for CHB treatment, and to determine which of them have stronger evidence-based data.

METHODS

Study Identification

This review was restricted to the TCPMs listed in the 2009 State Food and Drug Administration (SFDA) website (http://www.sda.gov.cn). We first searched for studies using any form of TCM therapy for CHB before screening for interventions that included drugs in the

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This study was supported by Hunan Natural Science Foundation (09JJ3065).

database of registered TCPMs at SFDA. In addition, we conducted searches using the drug names as key words to find potential missing trials for each drug.

Five reviewers (Zhang Tao, Wei Xing, Chen Ze-qi, Wang Dong-sheng, and Dai Xing-ping) independently searched the MEDLINE database (1966 to December 2009), EMBASE (1980 to December 2009), and CBM-disc (China Biological Medicine Database, 1979 to December 2009). We used a very sensitive strategy to identify all possible studies. The searching terms were: a) traditional Chinese medicine (TCM); b) Chinese herbs; and c) chronic hepatitis B. We searched the SFDA website using all drug names acquired from retrieved studies to determine whether the drugs were in the list of TCPMs registered by SFDA. We also identified additional studies by searching the reference lists of all the relevant articles using Google and then contacting the manufacturers. The latter measure was to acquire information on additional published and unpublished studies.

Study Selection

We selected the alleged randomized controlled trials (RCTs) for all of the TCPMs for CHB listed on the SFDA website. The trials were double blinded, single blinded or non-blinded.

Trials that enrolled patients of any age, sex or ethnic origin with CHB were eligible. The diagnosis of CHB was defined as serum HBsAg positive persisting six months or more, accompanied by elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) or with recurrent fluctuation, whether symptomatic or symptomless, and with or without liver biopsy findings compatible with chronic hepatitis.[5] Trials of subjects with super-infection or co-infection of CHB with another hepatitis virus were excluded.

The mode of intervention could be a single TCPM compared with placebo or no intervention, or regular non-specific treatments such as vitamins, or interferon-α (IFN-α) treatment (no limitation regarding IFN type or IFN treatment regimen), or nucleoside and nucleotide analogues. Combinations of a TCPM with another treatment compared with the same treatment were also included.

The trials that met the above criteria were included regardless of treatment duration or dosage. The primary outcome measures were evaluated, including: 1) mortality; 2) occurrence of hepatocellular carcinoma or liver cirrhosis; 3) loss of serum HBeAg; 4) seroconversion of HBeAg to HBeAb (antibody against HBeAg); 5) loss of serum HBV DNA; 6) loss of serum HBsAg; 7) normalization or decrease of ALT and/or AST levels; 8) liver histological recovery; 9) serum markers of liver fibrosis including hyaluronic acid (HA), type IV collagen (IVC),type III procollagen (PIIIP), and laminin (LN); 10) quality of life; and 11) adverse events.

Quality Assessment and Data Analysis

Three reviewers (Zhang Tao, Wei Xing, and Dai Xing-ping) independently selected trials that met the inclusion criteria and extracted the study details, which included randomization, allocation concealment, blinding, intention-to-treat analysis, case dropouts lost to follow-up, patient data, methods, interventions, and outcomes. Authors were contacted, if needed, to obtain information beyond that contained in the published papers.

The extracted data within a comparison was estimated if there were RCTs with similar quality available. If possible, we performed data analysis in conjunction with the Review Manager 5 (The Cochrane Library).

RESULTS

General Study Characteristics

Using our search strategy, we found 62 TCPMs registered by SFDA, with 138 available RCTs or quasi-RCTs, all of which were published in Chinese language journals and conducted in China from 1991 to 2009 (see Table 1 and Figure 1). The age of patients ranged from 2 to 84 years. More males were included in each study than females. The sex proportion of the subjects varied remarkably (3.89:1 to 1.93:1).

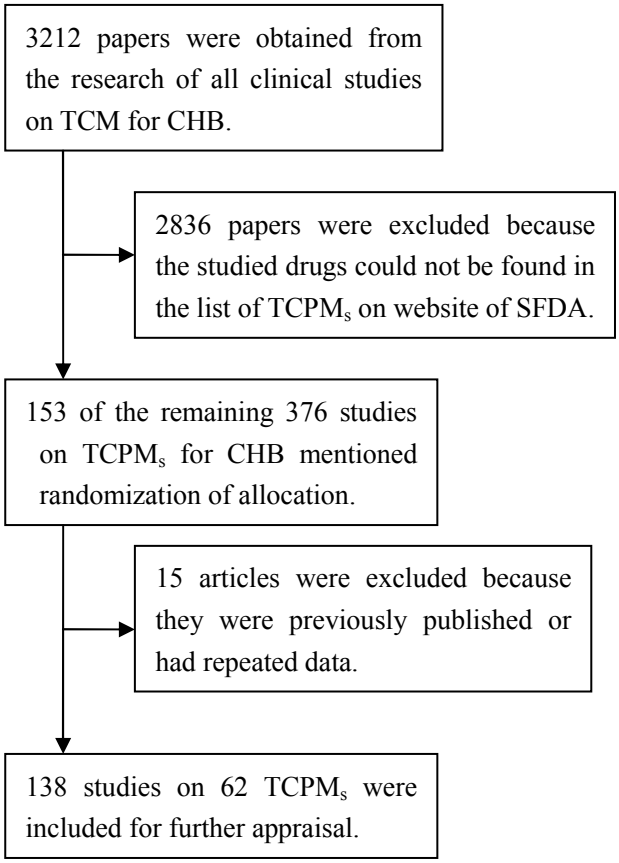

Figure 1. Flow chart of inclusion and exclusion criteria, and study selection.

One hundred and thirty-two trials (95.65%) applied the national diagnostic criteria for CHB in different time periods (from 1980 to 2005), but were essentially the

same. The remaining 6 studies had no clear diagnostic criteria. The duration of HBV infection before treatment varied from 6 months to over 30 years. The total duration of treatment with TCPMs varied from 3 weeks to 1 year. The dosage forms of the included TCPMs were pill, tablet, injection, granule and liquid. The intervention modalities were a TCPM compared with other agents, and a TCPM plus an anti-viral agent or non-specific treatment compared to the same treatment in a control group.

Table 1. The Included RCTs or Quasi-RCTs on 62 TCPMs, and subjects.

TCPMs	RCTs or quasi-RCTs	Patients	TCPMs	RCTs or quasi-RCTs	Patients
Dan Shen agents	15	1408**	Gan De Zhi (tablet)	1	300
Da Huang Zhe Chong pill/capsule	9	817**	Gan Long capsule	1	28
Shuang Hu Qing Gan granule	7	1106**	Gan Luo Xin capsule	1	123
An Luo Hua Xian pill	6	556*	Tan Re Qing injection	1	60
Ye Xia Zhu capsule	6	496	Xiao Zhen Yi Gan tablet	1	60
Huang Qi injection	5	546*	Yu Jin injection	1	38
Fu Zheng Hua Yu capsule	5	494	Fu Fang Mu Ji granule	1	126
Fu Fang Bie Jia Ruan Gan tablet	4	346	Chui Pen Cao granule	1	300
Cao Xian Yi Gan capsule	4	958**	Da Huang injecting	1	290
Hu Ju Yi Gan capsule	4	662*	Gan Fu Le (tablet)	1	58
Wu Ling Dan pill	4	509*	Li Gan tablet	1	45
Dang Fei Li Gan Ning capsule	3	283	Li Gan Long (tablet)	1	83
Liu Wei Wu Ling pill	3	658*	Ling Zhi capsule	1	60
Qiang Gan capsule	3	208	Huang Xuan Yi Gan granule	1	124
Fu Gan Kang granule	3	558*	Bie Jia Jian pill	1	164
Fu Fang Ku Shen injection	3	212	Fu Fang San Ye Xiang Cha Cai tablet	1	98
Gan Fu Kang tablet	2	550*	Xiao Yao pill	1	37
Gan Su granule	2	286	Wu Zhi capsule	1	84
Gan Shu capsule	2	135	Tui Hung Li Dan liquid	1	80
Qing Gan Li Dan liquid	2	159	Zhen Qi Fu Zheng capsule	1	60
Qing Kai Ling injection	2	462	Wu Ling Dan capsule	1	94
Xiao Chai Hu pill/granule	2	221	Bai Ling capsule	1	60
Yin Zhi Huang injection	2	135	Xue Sai Tong injection	1	102
Chao Yang pill	2	385	Fructus Lycii glucopeptide capsule	1	60
He Luo Shu Gan capsule	1	176	Deng Zhan Hua injection	1	50
Shu Gan Ning injection	1	80	Deng Zhan Xi Xin injection	1	100
Hu Gan Ning tablet	1	148	Yi Gan Ning granule	1	138
Jia Qi Gan Xian granule	1	407	Lentinan tablet	1	82
Ke Huang granule	1	82	Mei Hua Dian She pill	1	47
Gan Du Jing (granule)	1	104	Mai Luo Ning injection	1	125
Gan Yan Ling injection	1	90	Ao Tai Le granule	1	180

Notes: *Subjects>500 in total; ** Subjects>800 in total.

Study Quality Assessment

All of the included studies claimed randomization in the description of methods and case allocation. However, only nine studies[6-14] reported the correct methods of randomization (random numbers generated by computer or using random number table); but one trial[10] on the Fu Zheng Hua Yu capsule had a grade "A" level of adequate concealment of allocation because it allocated cases via random numbers generated by a statistics center which was independent from those conducting the trial. Six trials[8,10,15-18] mentioned the use of single or double blinding, but 5 of them[8,15-18] were missing the subject description. Only one trial[10] on the Fu Zheng Hua Yu capsule reported the participants lost to follow-up and used intention to treat analysis. The remaining 137 studies all neglected reporting patients lost and dropouts (Table 2). Interestingly, 116 studies conducted baseline data comparison between each pair of the experimental and control groups. All 116 studies reported good

baseline consistency despite the minority of studies with randomization methods.

Table 2. Studies of TCPMs with Jadad Score >1

Study	Intervention		Description for Randomization	Description for Blinding	Allocation concealment	Case Lost or Dropouts	Patients	Jadad score
	Experimental	Control						
Jin, et al.[6]	DS	SM	Randomized, Clear	Non-blinded	Unclear	Unreported	79	2
Yu[7]	SHQG+LAM	LAM	Randomized, Clear	Non-blinded	Unclear	Unreported	120	2
Shu[9]	SHQG+LAM	LAM	Randomized, Clear	Non-blinded	Unclear	Unreported	121	2
Qiu, et al[16]	SHQG + Vit.	Vit.	Randomized, Unclear	Single-blinded, Unclear	Unclear	Unreported	135	1～2♦
Hou, et al[8]	SHQG	YGQRJD	Randomized, Clear	Single-blinded, Unclear	Unclear	Unreported	206	2～3♦
Zhang, et al[15]	SHQG	YGQRJD	Randomized, Unclear	Single-blinded, Unclear	Unclear	Unreported	206	1～2♦
Liu, et al[10]	FZHY	HLSG	Randomized, Clear	Double-blinded, Clear	Clear	Reported	216	5
Liang[11]	FFKS	TMP	Randomized, Clear	Non-blinded	Unclear	Unreported	64	2
Xiao[12]	SGN	PMA	Randomized, Clear	Non-blinded	Unclear	Unreported	80	2
Qi, et al[13]	WLD	GSK	Randomized, Clear	Non-blinded	Unclear	Unreported	94	2
Yang, et al[14]	ATL	ZLGPK	Randomized, Clear	Non-blinded	Unclear	Unreported	180	2
Cheng, et al[17]	GS	BFD	Randomized, Unclear	Double-blinded, Unclear	Unclear	Unreported	72	2
Zhang, et al[18]	YGN	ONA	Randomized, Unclear	Double-blinded, Unclear	Unclear	Unreported	138	2

Notes: DS: Dan Shen injection; SM: Shen Mai injection; SHQG: Shuang Hu Qing Gan granule; LAM: Lamivudine tablet; Vit.:vitamins; YGQRJD: Yi Gan Qing Re Jie Du granule; FZHY: Fu Zheng Hua Yu capsule; HLSG: He Luo Shu Gan capsule; FFKS: Fu Fang Ku Shen injection; TMP: Thymopetidum injection; SGN: Shu Gan Ning injection; PMA: Potassium Magmesium Aspartate injection; WLD: Wu Ling Dan pill; GSK: Gan Su Kang capsule; ATL: Ao Tai Le granule; ZLGPK: Zhong Long Gan Pi Kang capsule; GS: Gan Shu capsule; BFD: Bifendate tablet; YGN: Yi Gan Ning granule; ONA: Oleanolic Acid.♦Studies were scored between 1 and 2, or 2 and 3 because the trials were single-blinding, not double-blinding as demanded by principle of strict RCT design.

Anti-viral Effects

Seventy-two (52.17%) of the included trials on 38 TCPMs observed the anti-viral effect for CHB. Of these forty-two (30.43%) on 27 TCPMs concluded that the TCPMs had some anti-viral effect. Twenty trials estimated the anti-viral effect of TCPMs plus a conventional anti-viral agent (Lamivudine, Adefovir, Dipivoxil, Entecavir, or IFN agents) compared with the same conventional anti-viral agent applied alone as control. The remaining 52 trials used TCPMs or TCPMs plus a non-specific treatment compared with a non-specific treatment as the control. Here, A non-specific treatment refers to regimens that were not considered to have any anti-viral activity, which in these reports included: 1) Diammonium Glycyrrihizinate; 2) Tiopronin; 3) Hepatocyte Growth-Promoting Factors; 4) Potassium Magnesium Aspartate; 6) Vidarabine; 7) Oleanolic Acid; 8) Silibin Meglumine; 9) Bifendate; 10) Thymopetidum; 11) Heparin Sodium; 12) Vitamins; 13) other TCPMs and Chinese herbal medicines.

Liver Function Protection

One hundred and twelve trials (81.16%) indicated that TCPMs protect liver function in terms of normalization or decrease of ALT or ALT/AST. One hundred and ten trials (79.71%) reported that TCPMs lowered the aminotransferase level, regardless of variation due to different dosage and duration of follow-up. The drugs used in the control groups largely varied among trials in each single TCPMs. Furthermore, 73 trials (52.90%) reported the detailed value change of ALT and/or AST while the other trials (28.26%) merely reported the normalization rate of ALT and/or AST level, or just stated ALT and/or AST level, without providing the actual value. This is one of the parameters that was estimated to reflect the overall efficiency of the TCPMs.

Twelve trials (8.70%) on 6 TCPMs reported liver histological recovery by liver biopsy. All 12 trials claimed that TCPMs improved liver histology. Five trials (3.62%) on 3 TCPMs used the Knodell histologic activity index (HAI) to reflect inflammatory activity, while the remaining 7 trials only mentioned having conducted a liver biopsy but did not provide detailed grades.

Anti-fibrosis Effect

Forty trials (29.99%) on 20 TCPMs reported an

anti-fibrosis effect of TCPMs. Only 1 trial (0.72%)[10] on the Fu Zheng Hua Yu capsule conducted liver biopsies to assess the fibrosis grades. The remaining 39 trials (28.26%) used serum markers (HA,IVC, PIIIP, LN) to estimate liver fibrosis. Different agents were applied either together with the TCPMs or as a control drug within the same study, which had more than one study included.

Quality of Life

None of the trials systematically evaluated quality of life. However, 128 trials (92.75%) reported the therapeutic effect of TCPMs in improving the symptoms of CHB, although no common evaluation criteria or scale was applied. The primary symptoms that could be improved by TCPMs were: 1) jaundice; 2) abdominal distension; 3) poor appetite; 4) hypodynamia; 5) splenomegalia; and 6) hepatomegalia.

Forty-one trials (29.71%) showed that mild adverse events occurred when treating with TCPMs. These trials suggested that TCPMs demonstrated good safety since no severe adverse events were verified during the trials or during follow-up. The remaining 97 trials (70.29%) did not state the occurrence of adverse events. Thirty-two trials (23.19%) conducted conventional tests such as routine blood, urine, stool, renal function, and heart tests (electrocardiogram). No obvious changes were reported relating to these tests. The reported adverse events were: 1) allergic reactions; 2) nausea; 3) constipation; 4) diarrhea; 5) dizziness; and 6) mild blood pressure change. All adverse effects disappeared without special treatment. Five drugs had one or more studies reporting a higher incidence of adverse events in the experimental group than the control group (Table 3).

Table 3. TCPMs with at Least One Study Reporting Higher Incidence of Adverse Events than the Control Agents

TCPMs	studies	Experimental		Control		Adverse Reactions
		Events(cases)	Total(subjects)	Events(cases)	Total(subjects)	from TCPMs
An Luo Hua Xian Pill	1	12	121	4	59	C, D
Dan Shen agents	2	11	114	15	169	A, E
Fu Zheng Hua Yu capsule	1	9	164	5	112	C, D
Shuang Hu Qing Gan granule	1	4	167	2	154	B, C
Wu Ling pill	2	3	192	0	101	A, C, D

Notes: A: allergic reactions; B: nausea; C: constipation; D: diarrhea; E: dizziness.

Hepatocarcinoma, Liver Cirrhosis, and Mortality

No trial reported events of hepatocellular carcinoma, liver cirrhosis, or mortality.

Individual Drug Analysis

The TCPMs that are relatively promising for future research and clinical practice for CHB, were generally studies having more participants (>800 in total) or a little higher quality (Jadad score>2). These studies were analyzed to provide a more quantitative assessment.

Dan Shen Agents

Dan Shen (Salvia Miltiorrhiza) is a very popular Chinese herb prescribed mainly for vascular diseases, such as coronary disease and cerebral infarction. However, we found that Dan Shen agents had most of the RCTs for CHB among our selected TCPMs. Dan Shen was originally used for treatment of the syndrome "stagnation or heat of blood", manifested in a variety of diseases. Some experimental studies have demonstrated the pharmacological effects of Dan Sheng herb or its extracts on liver impairment.[19-23] The dosage forms used for Dan Sheng agents were injection (10 studies), pills (4 studies), and liquid (1 study). Seven trials, all with duration of treatment longer than 6 months, evaluated whether or not Dan Shen agents had an anti-viral effect. Three reported that Dan Shen agents improved HBV serum markers or HBV DNA levels, while the other four trials claimed no significant difference compared to controls. Twelve of the 15 studies reported that Dan Shen agents may significantly improve ALT and/or AST levels. Five studies reported that Dan Shen agents improved hepatic fibrosis, as monitored by serum markers. Fourteen studies stated that Dan Shen may help recovery from symptoms induced by CHB. Only one study[6], with Shen Mai injection as the control drug, reported that Dan Shen group had less improvement of the symptoms of hepatitis as well as serum aminotransferase levels. This study had a Jadad score of 2, whereas the rest all scored 14, which means it is the only definitive randomized trial on Dan Shen agents. Comparison of Dan Shen with Sheng Mai injection with respect to improvement of symptoms, yielded an odds ratio (OR) of 0.25 with a 95% confidence interval (95% CI) of 0.08 to 0.84. Using data from this single RCT, the standard mean difference (SMD) and its 95% CI when comparing ALT and AST changes were 2.03 [CI: 1.48, 2.59] and 1.13 [0.65, 1.62], respectively. In contrast, the RCT using Dan Shen injection reported favorable improvements in hepatic fibrosis serum markers, HA, IVC, PIIIP and LN. The SMD and 95% CI were -0.65 [-1.11, -0.19], -0.90 [-1.37, -0.43], -0.52 [-0.98, -0.06] and -0.71 [-1.18, -0.25] respectively. Because of the divergence of study quality, selection of controls, and drug combination, meaningful data synthesis could not be made from the 15 reports.

Da Huang Zhe Chong Pill/Capsule

The Da Huang Zhe Chong pill is a very famous Chinese herb formula that originated in the classic "*Jinguiyaolue*" by Zhang Zhongjing in the East Han dynasty. We

identified two dosage forms with identical composition of Chinese herbs. Unfortunately, no quality RCT was found in the database on this historical drug for the treatment of CHB. However, it already had nine possible RCTs (Jadad score <2) without any description of a randomization method and had a large number of subjects. No trial reported that the Da Huang Zhe Chong pill/capsule had anti-viral effects, by mono-administration and did not enhance the anti-viral effects of other conventional agents. Six trials stated that a Da Huang Zhe Chong pill/capsule had better efficacy in treating elevated serum ALT and/or AST levels, especially for hepatitis symptoms, and that non-specific control drugs or mono-therapy of conventional IFN-α. Five trials (413 subjects) testing Da Huang Zhe Chong pill/capsule plus non-specific drugs as the experimental intervention, reported that ALT levels significantly decreased after treatment in the experimental groups relative to control groups using the same non-specific drugs. The pooled SMD had a 95% CI of -2.23 [-4.21, -1.06] with a heterogeneity test: P=0.31, and I^2=21%. The most interesting finding from CHB Da Huang Zhe Chong pill/capsule trials may be its anti-fibrosis effects. That is, seven studies (633 participants) reported that compared with non-specific treatments, combining Da Huang Zhe Chong pill/capsules with non-specific agents significantly lowered serum marker levels of hepatic fibrosis. The pooled SMD and 95% CI of HA, IVC, PIIIP and LN were -0.98 [-1.31, -0.12], -1.21 [-3.01, -0.66], -1.54 [-3.21, -1.01] and -2.03 [-3.47,-0.96] respectively. Sensitivity tests were not justified due to the heterogeneity among the trials, so it was not significant for each serum marker (P>0.05, I^2<50%).

Shuang Hu Qing Gan granule

The effectiveness of Shuang Hu Qing Gan granules was outstanding in the 62 TCPMs assessed as there were 5 studies with a Jadad score >1. Two trials (241subjects),[7,9] with a Jadad score of 2, used an intervention mode of Shuang Hu Qing Gan granules together with Lamivudine, versus Lamivudine mono-therapy. Both studies reported that the combination of Shuang Hu Qing Gan granules with Lamivudine did not show better results in HBV serum markers and HBV DNA levels after a 1-year of treatment and another 1 year of follow-up, than that seen for Lamivudine mono-therapy. Interestingly, Shu's study [9] stated that this combination lowered the occurrence of YMDD HBV mutations after 1-year of treatment. The OR and 95% CI were 0.37 [0.15, 0.88] between the experimental and control groups. Another two studies (412 subjects), [8,15] with a Jadad score of 2–3, and 1–2, used Yi Gan Qing Re Jie Du granules, which is an unidentified TCPM in this review, and served as the control drug. The two studies reported that Shuang Hu Qing Gan granules had anti-viral effects, and improved the serum aminotransferase levels and hepatitis symptoms. The pooled OR and 95% CI of HBeAg negative seroconversion were 3.83 [1.08, 13.61] with a significant heterogeneity between the two studies (P=0.02, I^2 =82%). The pooled SMD and 95% CI were -0.36 [-1.06, 0.34] with significant heterogeneity (P=0.009, I^2=91%) in ALT changes, and -0.37 [-0.96, 0.22] with significant heterogeneity (P=0.006, I^2 =87%) in AST changes. The pooled OR and 95% CI of improved symptoms were 2.92 [0.62, 13.75], with significant heterogeneity (P=0.006, I^2=87%). The remarkable heterogeneity might result from a divergence in study quality.

Fu Zheng Hua Yu capsule

The trail with Fu Zheng Hua Yu capsule was the only high-quality study[10] with a Jadad score of 5. The study was conducted exactly in accordance with the Consolidated Standards of Reporting Trials (CONSORT), Nine clinical centers and 216 subjects were involved in this single RCT. The study, with a 24-week treatment and a 12-week follow-up, did not exhibit the anti-viral effect of Fu Zheng Hua Yu capsule, whereas it did report improvement in liver function and hepatic fibrosis. The most valuable result of the trial was that this TCPM significantly improved liver impairment, as reflected by 93 liver biopsy samples—the gold standard of inflammatory fibrosis diagnosis. Biopsy samples treated with Fu Zheng Hua Yu capsule showed significantly lower grades on both liver inflammation (G) and fibrosis (S), than the control TCPM. The control He Luo Shu Gan capsule did not improve liver histology after the same duration of treatment, even though it is also a registered TCPMs identified in our systematic review. The OR and 95% CI of effective power on hepatic fibrosis were 3.58 [1.45, 8.79], which was consistent with the comparison of fibrosis serum markers with OR and 95% CI on effective power estimated 7.09 [3.89, 12.90]. The study also reported that Fu Zheng Hua Yu capsule had significantly better effective power on the ALT normalization than the control group, and the OR and 95% CI were 1.82 [1.03, 3.22]. No adverse event was found in the experimental group, whereas one case of a mild adverse event occurred in the control group. These results suggest a good safety profile of Fu Zheng Hua Yu capsule. The other four, low-quality studies, all with a Jadad score of 1, had similar positive results except for the anti-HBV effect.

Cao Xian Yi Gan capsule

Cao Xian Yi Gan capsule had 4 RCTs for CHB encompassing 958 subjects. Unfortunately, no study had a Jadad score >1. Three of them (780 participants) reported that this TCPM showed anti-HBV effect for a 6- or 12-month treatment. All 4 studies reported Cao Xian Yi Gan capsule had significant benefits, including elevation of ALT, and improving symptoms of hepatitis. Three of the studies (774 participants) used Fu Gan Ning tablet, and an unidentified TCPM identified in our systematic review, as the control mono-therapy. The pooled SMD of the 3 trials on ALT changes after a 4

week of treatment were -0.40 [-0.76, 0.09], with marginal significant heterogeneity (P=0.08, I^2=46%). The pooled OR and 95% CI of effective power on symptoms were 2.01 [1.27, 3.20], with marginal significant heterogeneity (P=0.14, I^2 =49%).

DISCUSSION

Infectious hepatitis B is a serious health problem in China. Among global deaths attributed to hepatitis B, approximately 40% occur in China.[24] CHB has become one of the hot topics of basic research and clinical practice of TCM.[25] Although various anti-viral agents have been used in China, doctors still tend to prescribe different kinds of TCPMs, considering the incomplete HBV clearance, drug resistance. and the high cost of western medicine.

This is the first comprehensive systematic review of government-approved TCPMs for CHB. Here, we restrict the category of TCPMs within a range of drugs for which the composition and use are based on the unique theory of TCM. This kind of theory may sound vague and irrational for most western medicine doctors. It is necessary to elucidate the mechanisms of TCM in terms of modern science and to standardize the dosage and clinical use of TCM. In fact, the integration of traditional Chinese medicine with western medicine has long been a state health policy in China. TCPMs play an important role in the policy, since under the guidance of traditional theories; TCPMs have a relatively stable quality control on the effective components via a series of pharmaceutical technologies and manufacturing management.[26, 27]

The methods of TCM treatment are based on the principle of the so-called “syndrome differentiation” (Bian zheng). The syndrome in TCM theory is closely related to the symptoms that the body presents, and refers to a natural philosophical determination on the overall status of the body. Different diseases sometimes have a common same syndrome in TCM. In China, TCPM prescriptions are made in accordance with the tradition of “syndrome differentiation”, which allows that the same TCPM can be used in treating various diseases. Considering the particular use of TCPMs, we first searched all studies evaluating any form of drugs in TCM and identified those with an experimental TCPM that was listed on the SFDA website. This approach was taken, rather than picking out names of some commonly used TCPMs as the firm search terms attempted to acquire sufficient studies for this review. The latter strategy actually may not be as sensitive as the former because some TCPMs that are usually prescribed for treatment of other diseases, may already have clinical trials that evaluated their efficacy for CHB.

For most clinical interventions, a prospective RCT is the best way to evaluate efficacy and safety.[28] We selected the alleged RCTs of TCPMs because they represent the best data when comparing with non-randomized trials. Assessment of methodology quality is the core mission of our systematic review, and the pivotal determination of whether or not the trials are reliable.[29-31] However, we found very limited evidence from the RCTs regarding the effectiveness of TCPMs. Only one trial on Fu Zheng Hua Yu capsule was viewed as a reliable RCT, which may support the finding that Fu Zheng Hua Yu capsule has a beneficial effect on hepatic fibrosis and inflammation. The majority of the RCTs identified were designed poorly according to the Jadad scoring method and appraisal on allocation concealment. For those reports that lack randomization and allocation concealment details, whether the randomization was conducted effectively is doubtful, since inappropriate randomization and allocation can lead to selection bias. Performance bias may also exist because most of the RCTs assessed were single-center and non-blinded. In addition, the lack of reporting case dropouts and those lost in the trials might result in attrition bias, which increases the overestimation risk for TCPMs. Therefore, the results obtained from these poor-quality trials are far from convincing and the TCPMs need to be further evaluated well-designed trials.

A large scale survey recently pointed out that among the authors who published clinical studies in Chinese language journals, there was a common lack of clear understanding of the methodological principles and a disregard for the scientific and social responsibility to use proper trial design.[32] Our review may actually support the conclusion of the survey. More particularly, we restricted the scope to government-approved TCPMs and anticipated that the average quality of those trials would be better. Unfortunately, the result of our quality assessment was still disappointing. There are two possible explanations accounting for the official admittance of TCPMs by SFDA, despite the fact that only a minority was properly designed regarding CHB. First, most TCPMs included may have good-quality studies for diseases other than CHB, given the fact that the use of TCPM is based mostly on “syndrome differentiation” and application to various diseases. Second, the approval of a TCPMs by SFDA is not strictly based on clinical trial data, but also on the history of the applicant, in addition to the low incidence of severe adverse events.

It is now clear that active HBV replication is the key driver of liver cirrhosis and hepatocellular carcinoma. Some TCPMs were reported to have some anti-viral effect. We sought to conduct a meta-analysis on two modalities: TCPMs versus non-specific treatment, and TCPMs plus TCPMs versus a conventional anti-viral agent. A “non-specific treatment” could be various drugs alone or in combination. We assumed that the anti-viral effect of TCPMs could independently appear when it was

not applied together with any anti-viral agents. Nevertheless, it was meaningless to perform meta-analysis on overall anti-viral effect because of the inadequate quality of the studies included. Moreover, we found an obvious divergence on the selection of control drugs and the intervention mode of the same drug, which led to the lack of eligible data for data synthesis, even if there had been no problem with the quality of source studies.

Most of the trials included reported that TCPMs could protect the liver from inflammatory damage as it lowered the level of serum ALT and/or AST. Only 12 trials conducted liver biopsies, which is considered the "gold standard" for assessing liver damage. Another interesting finding was the reported therapeutic effect of TCPMs on liver fibrosis as determined by serum marker (HA, IVC, PIIIP, LN). Current research supports that idea that hepatic fibrogenesis is a common result of injury to the liver. It is believed to be a key factor that leads to hepatic dysfunction and may also be important in portal hypertension.[33] This anti-fibrosis effect may be a potential benefit of TCPMs.

Five drugs (Dan Shen agents, Da Huang Zhe Chong pill/capsule, Shuang Hu Qing Gan granule, Fu Zheng Hua Yu granule and Cao Xian Yi Gan capsule) were selected for individual analysis as they either had been studied with large sample sizes or with relatively better quality. These TCPMs have stronger current data in the literature relative to others. Data synthesis was conducted in spite of the low quality trial design so as to provide a more quantitative understanding for the validity of these drugs, rather than to provide any guidance for selection of TCPMs in clinical practice. Nevertheless, Fu Zheng Hua Yu granule should still have privilege of first consideration by doctors because it has a moderate scale, multi-center, prospective and well-designed RCT documenting efficacy and safety.

Few adverse events have been reported in the included studies, which suggests that TCPMs are safe and nontoxic. However, this conclusion is still preliminary because there are no studies with sufficient long-term follow-up or sensitive toxicity tests. Several studies on the toxic and harmful profile of TCM have been published,[34-36] which should remind us of being aware of the possible long-term and underlying TCPMs -induced adverse events.

In conclusion, a definitive determination of TCPMs validity cannot be made from our appraisal because of the unclear methodological quality of the trials identified. The data is too weak to recommend a TCPM as the standard treatment for CHB. We need more well designed clinical trials to evaluate the efficacy and safety of TCPMs. Therefore, improving the methodological quality of relevant clinical trials should be a high priority.

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(Received October 18, 2010)